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# Comparing national home-keeping and the regulation of translational stem cell applications: An international perspective<sup>☆</sup>



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## ABSTRACT

A very large grey area exists between translational stem cell research and applications that comply with the ideals of randomised control trials and good laboratory and clinical practice and what is often referred to as snake-oil trade. We identify a discrepancy between international research and ethics regulation and the ways in which regulatory instruments in the stem cell field are developed in practice. We examine this discrepancy using the notion of 'national home-keeping', referring to the way governments articulate international standards and regulation with conflicting demands on local players at home.

Identifying particular dimensions of regulatory tools – authority, permissions, space and acceleration – as crucial to national home-keeping in Asia, Europe and the USA, we show how local regulation works to enable development of the field, notwithstanding international (i.e. principally 'western') regulation. Triangulating regulation with empirical data and archival research between 2012 and 2015 has helped us to shed light on how countries and organisations adapt and resist internationally dominant regulation through the manipulation of regulatory tools (contingent upon country size, the state's ability to accumulate resources, healthcare demands, established traditions of scientific governance, and economic and scientific ambitions).

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<sup>☆</sup> Research into the regulation of stem cell science and semi-structured interviews have been held in the following countries: China, Japan, Thailand, South Korea, Vietnam, Taiwan, Europe, Malaysia and India. Archival research was done on the regulation in the USA.

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## 1. Introduction

Stem cell science is a controversial field of research with a huge potential market for therapeutic applications on a global scale (Department of Business Innovation and Skills (2011)). A hackneyed view of stem cell therapy provision regards the market of life science research and biomedical products – preparations of viable cells, delivered through one of possible devices, such as a syringe, and marketed commercially, requiring marketing permission in most countries – as deeply divided between a world dominated by advanced scientific institutions and a world of ‘rogue’ stem cell providers (cf <https://www.newscientist.com/article/dn19056-death-revives-warnings-about-rogue-stem-cell-clinics/>; <http://www.economist.com/node/15268869>). The former is depicted as ethical, sophisticated, scientifically advanced; the latter as unethical, profit-motivated and uninterested in scientific advance (Sipp, 2012; McMahon and Thorsteinsdóttir, 2010). But by defining the difference in moral terms, critics do not do justice to the efforts of many researchers involved in stem cell therapy research and provision, for example, in Asia. In fact, we can discern only a few players that can afford to conduct clinical trials in tightly regulated research fields in ways that match the ideals of the dominant international science community, and only a few corrupt so-called ‘snake-oil providers’ (Sleeboom-Faulkner, 2014). Instead, a very large grey area of stem cell-related activities exists in which stem cell scientists, doctors, politicians and regulators accommodate, adjust, circumvent and alter regulatory spaces to help advance clinical research in ways that suits their circumstances.

The current use of the binary between bona fide science and snake oil traders has its roots in a situation in which a few international organisations and countries driven by members from well-funded, cautious research laboratories set the standards. Those that do not stick to agreed conventions are seen as undisciplined and fraudulent (Sipp, 2012; Bharadwaj and Glasner, 2008). This binary has led to the tainting of a large group of under-resourced researchers, and to one-sided portrayals of their aims. Scientists delineate themselves from the ‘science’ of other scientists, claiming scientific integrity for themselves. Although this ‘boundary work’ is inherent to the scientific community (Gieryn, 1983; Gilbert and Mulkay, 1984; Salter and Qiu, 2009), it is now played out on a global level, expressed in papers on ‘research ethics’ and ‘good practice’ at international scientific conferences.

Recent years have seen a new regime of coordination of medical practices linking medicine and biology together that has led to the increased articulation of genomic biology, multicentre clinical trials, organised patient communities, and biobanks, which depend on sophisticated laboratories, reliable instruments and devices that produce exchangeable results. Standard setting, guidelines and regulation are central to this regime. Thus ‘regulatory objectivity’ (Cambrosio, Keating, Schlich and Weisz, 2006) defines the contents of what the dominant science community regard as correct practices (Birch, 2012). These standards are often conventions: what counts here is that results are compatible with other laboratories, whereby ‘truth’ and ‘accuracy’ become dependent on these conventions. In regenerative medicine (RM), referring to research and therapies using the regenerative powers of the body, the International Stem Cell Initiative (ISCI), for example, has taken the initiative to define pluripotency and assays, and the media and reagents used to produce them (Eriksson and Webster, 2008). Standards do not only facilitate exchange, they can also define the clinical criteria in terms of diagnosis. Thus, scientific standards and assays for mesenchymal stem cells are critical both to the advancement of scientific development and clinical practice (Bianco et al., 2013). Crucially, the exchangeability and common use of data require the deployment of similar equipment, devices and

assays. This has major economic and intellectual property rights (IPR) implications to the advantage of those that set the standards, and to the disadvantage of the reputation of researchers that cannot comply with them (PRNewswire, 2014; Birch, 2012).

These developments pressurise scientists all over the world to follow the standards of elite laboratories. At the elite levels, scientific knowledge is sanctioned by international peer-reviewed journals, regulation vetted by expert committees in modern bureaucracies, and novelty defined by IPR. Here, political discourses on norms and values define the ethics acceptable to a small number of societies (Timmermans and Epstein, 2010; Birch, 2012). International collaboration, then, requires elite laboratories in most countries, including those with few resources, to demand regulations that enforce ‘global’ standards. But the necessity to purchase costly equipment and resources has also led to resistance against regulatory norms and standards by those less well endowed (Sleeboom-Faulkner, 2013).

Insight into this friction between compliance and resistance is complicated by an ever-increasing demand on scientific leaders to be familiar with research regulation and research ethics, multiple scientific fields, IPR, methods of team management and business strategies, leading to development of ‘bioentrepreneurship’, ‘bio-networking’, and ‘international entrepreneurship in the life sciences’ (Jones et al., 2011: 2; Sleeboom-Faulkner and Patra, 2011) engaging with coordinative activities and methods using local knowledge resources and international connections. Here, values and methods are constantly weighed to realise the desired kind of ‘local’ model of scientific decision-making, considering, for example: the cost, feasibility and aptness of the ‘right’ number of patients used in investigational studies or clinical trials; the quality of preclinical studies and toxicity studies; the fees charged for investigational studies using unauthorised stem cell products; and the ways of marketing therapy products. Global variability of therapy marketing and patient demand complicates the picture of compliance and resistance even further (Petryna, 2009; Chen and Gottweis, 2011). This variability has resulted in a situation in which the relationship between patients and doctors is conditioned by availability of research funding, expertise and medical facilities, as well as collaborative networks and regulatory constraints.

### 1.1. National home-keeping

At the intersection of the international and local governance of stem cell science, we locate a form of decision-making, which we refer to as ‘national home-keeping’. National home-keeping is a heuristic notion we use to capture policies designed when countries face universal standards, often created ‘elsewhere’, that are not conducive to local policies of economic, health and scientific development. In this article, we illustrate how policies of national home-keeping condition stem cell innovation through regulation and regulatory instruments.

This article follows global assemblage approaches (Ong and Collier, 2005; Sleeboom-Faulkner, 2014) that avoid assuming an encompassing global force or a pre-existing local path, but investigate the dynamic interactions among international, regional, and local politics. Although various works in particular on human embryonic stem cell research have appeared in a global setting (Thompson, 2013; Gottweis et al., 2009; Webster, 2013; Zhang, 2012; Bharadwaj and Glassner, 2008; Sleeboom-Faulkner, 2014), issues discussed in these works regard the status of the embryo and gamete donation rather than issues of clinical applications.<sup>1</sup>

<sup>1</sup> Thomson in her book on embryonic stem cell research discusses ‘stem cell tourism’ (Thompson, 2013), but the therapy is only provided by Geeta Shroff’s NuTech Mediworld, India, as such. See <https://amandaboxtel.wordpress.com/contact-dr-geeta-shroff/>.

Nevertheless, several of these works have emphasised the importance of analysing RM in the context of globalisation, global politics and global governance (Thompson, 2013; Gottweis et al., 2009). These and other works (Salter and Qiu, 2009; Salter et al., 2015; Thompson, 2013; Bharadwaj and Glasner, 2008) have especially focused on the central role of bioethics in the brain drain and global dynamics of stem cell science. Some (Salter et al., 2015; Cooper, 2008) have emphasised the centrality of global competition and hegemony in the global dynamics of stem cell development, whereby bioethics and stem cell governance has become a pawn in a global race. This article, however, emphasises the importance of the dynamic interaction of global regulatory changes between and within countries, including radical regulatory changes in Japan and South Korea, regulatory crises in China and India, gradual reform in the EU and the USA. These, we argue, derive from policies that aim to enable scientific innovation at home, and are intimately linked to the emergence of new international movements.

Our views differ from other works discussing translational RM in a global context, as it is more comprehensive and systematic in pointing out, not so much the influence of political cultures of governance, but the specific circumstances of different countries that variously condition the adoption of particular regulatory policies. Rather than taking the political and bioethical cultures of nation-states as following global powers, this article uses the notion of ‘national home-keeping’ as a heuristic tool to analyse the ways countries deal differently with the standardisation of research. Rather than accommodating what are regarded as bona fide global guidelines, national home-keeping policies articulate international regulatory trends with home conditions comprising competing local views and interests to enable innovative research applications. As a result of both regulatory diversity and dissatisfaction with national home-keeping policies, we argue, scientists have organized themselves in networks that recommend different sets of regulatory guidelines both at home and in a global context.

## 1.2. Methodology and conceptual overview

Our research on translational stem cell applications builds on over three years of research across Asia, Europe and the US, using both local languages and English to communicate with interviewees and read written resources. The research set out to examine different local and regional translational stem cell research practices. Interviews with regulators, scientists, medical professionals show that modes of regulation and ISSCR guidelines play a central role as main reference points in understandings of translational stem cell research. Discussing differences in international regulation and local translational science, interviewees consistently referred to regulatory dimensions of authority, permissions, regulatory space, acceleration of regulatory pathways and implementation as main research issues and factors. Our research has found a link between the national development of regulatory tools mobilized in home-keeping policies and the national conditions they build on, which we correlate with policies aimed to enable local development of the field. We discuss examples of locally mobilised tools in Part II, with the exception of ‘implementation’. We analyse ‘implementation’ in Part III together with the pattern we delineated in home-keeping policies of the countries examined. This pattern is based on the kind of regulatory policies over six years (2008–2014): adjustment, radical change, impasse and early formulation of regulation (see Table 1). The identification of this pattern, in turn, led us to analyse the similarities and difference between countries with divergent home-keeping policies, the results of which we outline in Part III.

Part IV discusses how, as a result of the existent diversity of

regulation and dissatisfaction with national home-keeping policies organisations and networks have emerged that champion very diverse international guidelines and standards. We discuss their activities, questioning the designation of ‘international’ in this context.

Field methods used include semi-structured interviews and/or archival research carried out by the authors across Asia and in the UK between 2011 and 2015. The materials presented draw on interviews with regulators, company managers, scientists, medical professionals and patients (see Appendix) and six workshops on translational stem cell applications and patient needs in London, Brighton, Seoul, Beijing, Bangalore and New Delhi. Interviews were analysed by repeated readings, thematic content analysis, identification of significant examples, and the abductive method (Timmermans and Tavory, 2012) for exploring the ‘home-keeping’ concept. One co-author was a member of the UK’s government-advising Regenerative Medicine Expert Group (RMEG) during 2014 and attended European Medicines Agency Committee for Advanced Therapies Interested Parties meetings, both further data sources. The data presented are anonymised and the names of interviewees are pseudonyms. All interviewees cited in this article have been informed of the research and have consented to be interviewed for this study. The research was approved by the ethics committee of the University of Sussex and King’s College London.

## 2. National home-keeping and regulatory policy-making

National home-keeping policies direct the development of science to articulate international regulatory trends with socio-political and economic policies and home conditions. Developments in cell therapies are subject to changes in science policies, science funding and science regulation. The effectiveness and reach of science regulation, however, can be steered in many ways, for example, by assigning a particular level of authority to regulation, through funding-linked incentives, such as research review, scientific protocols and research ethics, and through permissions, such as for investigational studies/trials, experimental research spaces for research involving human subjects and marketing licenses. In this section, we discuss how innovation for stem cell therapies in particular is conditioned through regulation in Asia and in EU and the USA. Apart from in the first subsection, we focus on the EU and USA to indicate the variability in regulatory provisions in the part of the world often associated with advanced science and technology. It also serves as a reference in discussing national home-keeping in Asia in Part III. The section sketches the variety and flexibilities of the regulatory landscape in terms of authority, permission, space and acceleration, embodied in policies of ‘national home-keeping’.

### 2.1. Regulatory authority

National home-keeping policies can condition regulatory tools. Thus, countries might diversely regulate the development of stem cell applications by legal means (hard law), formally sanctioning violation, or through guidelines, that is, soft law. Some countries, such as Japan, until recently, have predominantly used soft law, which can be very effective when social/institutional controls are available at the ground level (Ida, 2002).<sup>2</sup> Other countries make use of a range of regulatory levels with varying degrees of authority. For instance, China has laws (法), administrative regulations (行政法规), departmental regulation (部门规章), ethical principles (伦理原则)

<sup>2</sup> The law on therapeutic cloning (Sleeboom-Faulkner, 2011a) and the 2013 regulation for cell therapy (see below) are seen as exceptions.



**Table 1**  
Pattern of regulatory policy-making.

	Traditionally scientific leaders	Large LMICs	Scientifically advanced Asian countries	Small LMICs
Regulatory adjustment	US/EU			
Sustained regulatory impasse		India/China		
Radical changes in regulation			Japan, South Korea	
Unclear/developing regulation				Malaysia Vietnam Thailand

and administrative measures (管理办法) (also see Wahlberg et al., 2013). New regulation usually comes out as draft (草案) or trial regulation (试行), amenable to change. In addition police and armed forces have their own regulation for scientific research and medical treatment in hospitals and research centres.

In Europe and the USA we see major differences in the organisation of regulations and the status assigned to different forms, with traditionally a relatively high reliance on soft law in Anglo-American countries compared to continental Europe. For example, the UK is well known to have a highly regulated system but liberal laws for stem cell research, while France is the opposite. Furthermore, national authorities implement the European Medicines Agency (EMA) regulations through varying national regulatory and/or legal mechanisms. In the USA, the Food and Drug Administration (FDA) regulates translational stem cell research federally, but leaves powers to the private sector and state governments. Finally, the status and authority of regulatory organs are subject to constant innovation, as will become clear below. The political and legal status of regulation is crucial in understanding its impact.

## 2.2. Permissions for investigational studies – geographic dimensions

Innovative stem cell treatment in most countries requires permission from a local institutional review board (IRB) or equivalent and from a higher-tier organisation at provincial or national level. Nevertheless, specific requirements can differ substantially per country. Scientists who are aware of this can decide to collaborate strategically (Sleeboom-Faulkner and Patra, 2011) to enjoy advantageous regulatory conditions. This might require collaborative partners to comply with international guidelines, including Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP), and ethics review. In some countries, local conditions for permission for clinical studies clash with national science policies, whereby the former encourages and the latter curtails clinical applications. For instance, the Guangzhou municipal government in southern China had funded translational stem cell applications discouraged by the national government (Interview X, 25–4–13/Guangzhou; P, 28–4–13/Guangzhou).

In some countries, national permission for the clinical application of stem cell products may only be necessary for marketization. This means that hospitals can provide treatment using unauthorised stem cell products as long as they do not charge for the stem cell products; they charge for the 'service'. Alternatively, stem cell products are applied off-label for indications without evidence for their safety and efficacy. Such methods enable clinics in the USA, China and India to continue to provide treatments that have not been recognised at home (Richer, 2011). In the USA permission can be acquired to take an experimental drug across state boundaries. Thus, through the Investigational New Drug (IND) programme in the USA, a pharmaceutical company can obtain FDA permission to ship an experimental drug across states (usually to clinical investigators) before an application for marketing a drug has been

approved (US FDA, 2014a). This possibility opens up a large pool of potential subjects for clinical trials.

## 2.3. Creating spaces for procurement of innovative treatment and experimentation

Apart from following the pathway of clinical trials, there are other ways of making innovative treatments available. One is compassionate treatment, a term usually referring to a last-resort treatment for individuals without other options, also used by researchers who do not have permission for clinical trials. Thus, the Indian company Neurogen justifies stem cell therapy provision for Duchenne muscular dystrophy (DMD) and other conditions by appealing to compassionate use as cited in section 37 of the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects,<sup>3</sup> which states that doctors may use experimental therapies when no other treatment is available (Sharma et al., 2014: 236). The US FDA allows only a very few cases of compassionate treatment exemption, as researchers can charge patients (Cyranoski, 2011), while the EU regulates compassionate treatment separately from research.

The EU's Advanced Therapy Medicinal Products (ATMP) Regulation (Article 2[2]) provides the Hospital Exemption (HE) clause, which allows member states to facilitate 'non-routine use' for individual patients in the absence of a marketing authorisation (European Commission, 2014). The uneven implementation of the HE due to different interpretations in European countries, however, has led to a broad use of the clause, and it is feared that it deters users from applying for market authorisation for ATMP. For instance, while TiGenix developed cartilage treatment by going through the central regulations, others used the HE for similar treatment indications (House of Lords (2013): 544). The pre-existing UK's 'Specials scheme', which is covered by Article 5(1) of Directive 2001/83/EC, allows for the manufacturing and provision, including import, of unlicensed medicines for the treatment of rare disease and the use of drugs for individual patients' unmet needs (Lowdell et al., 2012; Mahalatchimy et al., 2012). It can be scaled up and used across Europe, with the manufacturer paying for the process rather than the product (MHRA, 2007; European Commission, 2014).

Applications can receive extra incentives in terms of fees and priority at any stage of the development of therapeutic products through the Orphan Drug Designation (ODD) if certain 'rare disease' criteria are met. For instance, Multi-Stem, a US-based company, which created a graft versus host disease (GvHD) prophylaxis for leukaemia patients receiving allogeneic (from others) haematopoietic stem cells (HSCs), has received ODD both from the FDA and EMA for its allogeneic multipotent adult progenitor cell based 'MultiStem therapy' (Athersys Inc., 2013).

<sup>3</sup> See <http://www.wma.net/en/30publications/10policies/b3/>.

<sup>4</sup> Compiled by the main author with assistance of the co-authors. The figure was empowered by Gliffy software embossed onto 'outline-world-map' ([www.outline-world-map.com](http://www.outline-world-map.com)).

#### 2.4. Acceleration of translational pathways

In the EU, some stem cell products may be used clinically without marketing licence. This, however, does not mean that they are uncontrolled, as is illustrated by the ODD, HE and Specials, pathways, which essentially assign spaces of development. In addition, accelerated licensing routes are possible under certain conditions. In 2012, the US Congress passed the FDA Safety Innovations Act (FDASIA). Section 901 of FDASIA amends the Federal Food, Drug, and Cosmetic Act (FD&C Act) to allow the FDA to accelerated approval for drugs for serious conditions that fill an unmet medical need, using a surrogate or an intermediate clinical endpoint (also see, [US FDA, 2014c](#)). Post-marketing confirmatory trials are generally required to verify and describe the anticipated clinical benefit or effect ([US FDA, 2014b](#)). In the EU, the European Medicines Agency (EMA) has integrated a number of initiatives, including adaptive trial design, named the Medicines Adaptive Pathways to Patients (MAPPs) programme, aiming to create an approval process that adapts quickly to a given patient's response to therapies, focusing on clearly defined patient populations with unmet medical needs ([EMA, 2014](#); [Ford et al., 2013](#)). However, no agreement exists yet about minimal standards of scientific evidence and reimbursement, and these initiatives do not sit within EU pharmaceutical or other law. In the same vein, in the UK the MHRA has piloted the Early Access to Medicine Scheme ([MHRA, 2014](#)) 'to support access to unlicensed or off-label medicines in areas of unmet medical need'. It uses a Promising Innovative Medicine (PIM) designation, similar to the Breakthrough Therapy designation in the USA, and will involve collaboration between existing institutions, such as the National Institute for Health and Care Excellence (NICE) and the National Health Service (NHS) ([MHRA, 2014](#)). The data requirements for a PIM are less than those for a formal marketing application dossier. A more fundamental approach to market acceleration took place earlier in South Korea and Japan, where Biologics License Applications (BLAs) are conditionally provided for new investigational drugs after producing evidence of safety and plausibility of efficacy (see below). Researchers in the USA and in Europe, on the one hand, are concerned about the consequence of using 'deviant' standards and regulatory norms and, on the other hand, worry that they are losing a competitive edge ([Freeman and Swidlicki, 2014](#)).

To summarise, overall we can see a wide variety of ways in which different countries, notably the US and EU, have been introducing a range of different, limited, flexible measures, some hard law some soft, some within legal regimes some extra-legal, designed to enable the authorisation and mandating of innovative stem cell (and other cell) technologies, while maintaining their core commitment to traditional biomedical standards and methodologies and their related regulatory and institutional cultures which support highly innovative bioeconomic stem cell science entrepreneurship.

### 3. Patterns in national home-keeping

Our comparison of the performance of national home-keeping policies across countries has enabled us to identify correlations between regulatory policies and the situational conditions of countries in a global context. The intentions behind regulation can be difficult to verify. We therefore need to gauge its political meaning from the context of overall trends in scientific infrastructures and institutional cultures in countries to improve our understanding of regulation performance ([Sleeboom-Faulkner, 2011b](#); [Faulkner, 2012](#)) in particular political contexts.

Local regulation takes into account infrastructural factors such as the supply of working electricity, affordable reagents, training for technicians, public communication channels, and a modern

administration. In India, the absence of a responsive bureaucracy has frustrated scientists who have applied for National Apex Committee (NAC) permission to conduct clinical trials (interview, B, 06/08/2013-India; personal communication G, 11/11/14-UK). In many countries, applying for permission for clinical trials is left to the individual institution. In India, an official from the Indian Council for Medical Research (ICMR) said that audits might never reach those institutions that have not applied for permission (interview N, 18/09/2012-IN).

A shared scientific culture is needed to indicate what is acceptable in stem cell product applications. But in China and India interviews show that sharp conflicts developed between local funders of stem cell product applications and the national government over the conditions under which they may be used and marketed. In Thailand, Japan, South Korea and Taiwan, we regularly found stem cell products on offer as cosmetic cell therapy or as holistic medicine. Disagreement about the interpretation of key terms can undermine effective regulation. One example is the meaning of 'minimal manipulation' of stem cells. In the USA the companies RNL/Celltex and the FDA disputed whether the expansion of stem cells constitutes minimal manipulation, falling under the medical practice law (regulated by Texas), or whether it should be treated as a biological drug, regulated by the FDA ([Cyrnoski, 2013a](#)). Another example is the contentious interpretation of the 'non-routine' use of stem cell products for individual patients authorised through the EU Hospital Exemption ([EBE, 2011](#)). A last example from Thailand relates to the term 'stem cell therapy', whereby the notion of 'stem cell' indicates that it requires state authorisation. To avoid criticism, companies advertise the application of unauthorised stem cell products as 'cell treatment' ([Chaisinthop, 2014](#)).

The 2013 overview of stem cell and genetic engineering products with marketing permission in [Fig. 1](#) gives a general idea of how countries make regulation work for innovation in RM. As will become clear below, this figure does not represent so much the scientific advancement or productivity in RM of a country, as it does the kind of regulatory policies it has adopted.

#### 3.1. Wealthy, traditional leaders of scientific development and regulation

Until recently, the USA and EU have insisted on following scientific regulation for developing stem cell technology based on the traditional preclinical testing and clinical trial model, although as described above this translational paradigm itself is increasingly open to various, limited flexibilities. While clamping down on therapies using unauthorised stem cell products regulatory spaces have been created for promising stem cell technologies. Some of these regulatory spaces are of a local nature, and entail the high costs, bureaucracy and time needed for the pathway of randomised control trials (RCTs), as well as investigational research using a small number of available human subjects. The following subsections discuss initiatives that organise and standardise stem cell research in Asia, *contra* the US/EU cases, whose regulation we have characterised above as adjusting incrementally.

#### 3.2. Large and scientifically ambitious low- and middle-income countries (LMICs) (India, China)

Large and scientifically ambitious LMICs, such as India and China, pool resources to develop a life science industry, though they can afford only a limited number of high-tech laboratories per head of the population. Influential commercial actors play a leading role (e.g. Stempeutics and Reliance in India; Beike Biotech and Zhongyuan Union Stem Cell Bio-engineering Corporation in China). Apart from well-equipped commercial actors, both countries have a

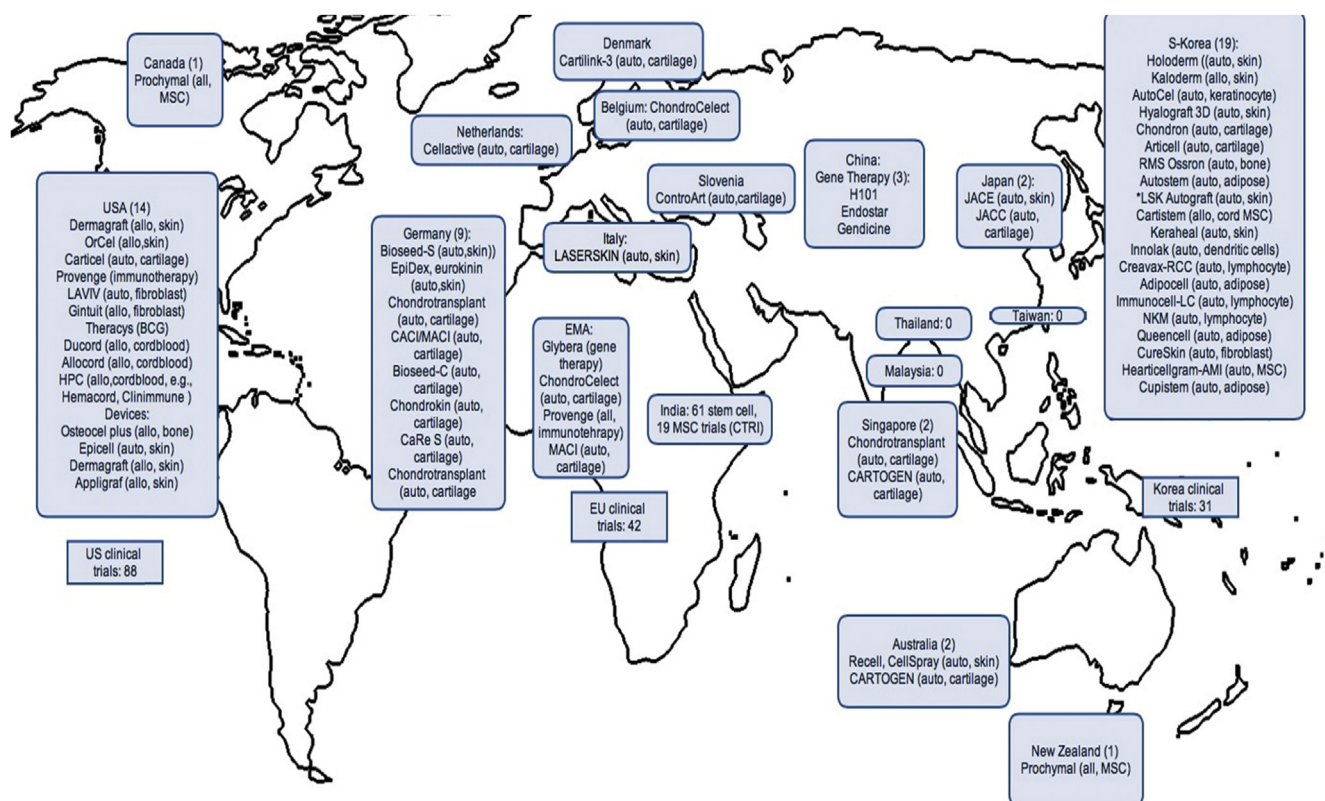


Fig. 1. Stem cell and genetic engineering products in 2013.<sup>4</sup>

large body of underequipped laboratories using localised standards, skills and collaborations. Stem cell therapy enterprises linked to hospitals are readily found on the Internet. In both countries local and national governments invest heavily in the life science industry, and a call exists for an 'ethics of return' in the form of benefits to patients. In this context, stem cell researchers are put under pressure not only to develop the 'world's highest-standard medicine', but also the 'world's first clinical applications'. Scientists in India and China express concerns about the recognition of their work, which are heightened as local scientists see that clinical experiments they started years ago are now part of clinical trials elsewhere without recognition of their contribution. This creates a dilemma for scientists and policy-makers (interviews X, 28/04/2012-China; H, 12/11/14\_UK).

### 3.3. Small LMICs (Thailand, Malaysia, Vietnam)

Small LMICs invest relatively little into infrastructural development and translational stem cell applications and have no concerted policy directing the research (Pérez Velasco, Chaikledkaew, Myint, Khampang, Tantivess and Teerawattananon, 2013; Saengpassa and Sarnsamak, 2012). For example, although Malaysia since 2005 has invested RM 3.2 billion in 225 so-called BioNexus-status companies through its Malaysian Biotech Corporation (Bionexus, 2014), its financial capacity into national stem cell science is clearly inferior to that of India and China.

Although regulation for local approval by an IRB and the national authorities in Thailand, Malaysia and Vietnam is in place (MoH Malaysia, 2013; TMC, 2009;<sup>5</sup> NIHBT, 2011), presumptions of

'loose regulation' make these countries targets for collaboration. Examples include the University of Texas MD Cancer Anderson Centre supporting clinical trials with bone marrow transplants in Bangkok (Bionews Texas, 2013); Japan and India's joint-venture Niscell, which provides autologous (from self) stem cell therapy and conducts clinical stem cell trials in Malaysia (Niscell, 2013); and India's Stempeutics' clinical stem cell trials in Malaysia (Stempeutics, 2013; Bionexus, 2014). Regulation of translational stem cell applications in these host countries tends to be brief and general, so that the conditions under which authorised clinical trials take place are unclear (TMC, 2009; MOH Malaysia, 2013; Thomson Reuters, 2015).

In Thailand and Malaysia, scientists and medical professionals expressed worry about the country's scientific reputation. Some clinics offer 'stem cell therapies' commercially, such as those attached to Beike Biotech and Wu Medical Centre,<sup>6</sup> while others, such as TheraVitae, and SiriCell, have closed down. Even when regulation prescribes the application for permission from a National Ethics Committee, clinics offer treatment using stem cell products commercially without. Examples are Cellport, VillaMedica, PatrLife, AbsoluteHealth, HolisticMedical Centre in Thailand<sup>7</sup>; StemCellMalaysia, StemLife, and WhatClinic in Malaysia.<sup>8</sup> In Vietnam, a late-developer in this field, hospitals offer commercial treatment using unauthorised stem cell products, and collaborate

<sup>6</sup> <http://www.unistemcells.com/more.asp?id=128>.

<sup>7</sup> <http://www.absolutehealthplus.com/adipose-stem-cell-therapy-tid67.aspx>; <http://www.cellportthailand.com/>; <http://www.holistic-medical.com/>; <http://www.patrlife.com/>; <http://www.villamedicathailand.com/>.

<sup>8</sup> <http://www.stemcellmalaysia.com/>; [http://www.stemlife.com/malaysia/corporate\\_information/history.html](http://www.stemlife.com/malaysia/corporate_information/history.html); <http://www.whatclinic.com/oncology/malaysia/stem-cell-therapy>; <http://doanhnhonline.com.vn/con-loc-te-bao-goc/>.

<sup>5</sup> Non-compliance may lead to the revocation of medical license (Medical Professional Act B.E.2525 (1982) Section 21 (3)).



with South Korean, Chinese and Singaporean companies, including RNL (renamed K-Stemcell), Asian Stem Cells, and KenCare.<sup>9</sup> In all three countries scientists and regulators worry that investment in RM does not serve the interests of the majority of patients (Saengpassa and Sarnsamak, 2012), who cannot afford the treatments on offer in the private sector.

#### 3.4. Scientifically advanced and ambitious medium-sized countries in Asia (South Korea, Japan)

Two scientifically advanced countries in Asia, South Korea and Japan, have reorganised their regulation to speed up the process of translational research by means of fast-track pathways for certain kinds of stem cell applications. To uphold safety, a complex form of implementable regulation has been devised, including standards for ethics, GMP/GLP, banking, permissions, market licensing, and follow-up treatment. South Korea's Regulation on the Review and Authorization of Biological Products introduced 'fast-track approval' (KFDA, 2010; MFDS, 2013). Thus, the Korean Food and Drugs Administration (KFDA) has eased its regulation on the use of autologous cell products over the last few years by granting exemption from submission requirements and exemption from phase I trial when the data have been published in professional journals (Notification 2011-225, 2011). Furthermore, the MFDS (which replaced the KFDA in 2013) allows post-marketing submission of documents concerning the efficacy for medicinal products for serious and life-threatening diseases, including AIDS and cancers, and when there is no other treatment option available (MFDS notification 2013-238, article 58). Not surprisingly, South Korea has been the first in approving stem cell products: Hearticellgram and Cartistem for Osteoarthritis and Cupistem for Crohn's fistula (Wohn, 2012), followed by many others (see Fig. 1).

Having been frustrated by its slow regulatory bureaucracy, and hoping to take induced pluripotent stem cells (iPS) to the clinic first, Japanese regulators and scientists confirmed that they looked to South Korean regulatory efforts to revise Japan's. In 2010, the Japanese government revised 'the guideline for clinical studies using human stem cells', expanded its coverage to clinical studies using embryonic stem cells and induced pluripotent stem (iPS) cells. In 2013, three new (hard) laws were introduced, of which the first, the Regenerative Medicine Promotion Act, was enacted in May 2013. It promises to promote RM among the Japanese population, linking state efforts with industry, and devising policies in support of bringing RM to the clinic. The second, The Act on the Safety of Regenerative Medicines, was enacted on 25 November 2014, and uses a three-tiered system based on risk-assessment to determine the level of required research oversight. In cases of high risk (involving pluripotent cells) and medium risk (involving somatic stem cells), medical institutions need to apply for permission from a special committee for RM identified by the Ministry of Health, Labour and Welfare (MHLW). The third, the Revision of the Pharmaceutical Affairs Law: The Pharmaceuticals, Medical Devices, and Other Therapeutic Products Act (PMD Act), enacted on 25 November 2014, stipulates that the Pharmaceuticals and Medical Devices Agency (PMDA) and the MHLW provides an expedited approval system for regenerative medical products. After the safety is confirmed and the results predict likely efficacy, the product will be given conditional, time-limited marketing authorisation (PMDA, 2014; Azuma, 2015). This radical regulatory reform, allowing

market authorisation before the provision of scientific evidence through clinical trial (Cyranoski, 2013b; Nikkei, 2014), has already attracted the interest of large companies, such as Athersys, Mesoblast, and Cytos Therapeutics (Market Watch, 2014). Also, companies from elsewhere in Asia, such as India's Stempeutics, consider approaching Japanese partners (interview J, 23/09/13-India). Nevertheless, considering the fear of scandal from the side of regulators, and the uncertainties around post-marketing conditions of cell products (interview K, 1/11/13, Japan), it might take some time before new stem cell products will be given marketing permission.

In short, our examination of the ways in which countries undertake boundary-work to harness the regulation of RM in an international context led us to categorise countries according to their size, the state's ability to accumulate resources, healthcare demands, established traditions of scientific governance, and economic and scientific ambitions (see Table 2).

As we have discussed, the traditional leaders in the field in the EU and USA have been adjusting their regulation to the demands of RM in piecemeal fashion. The ability of large LMICs to pool resources allows them to catch up with elite laboratories, but simultaneously these countries face regulatory difficulties in dealing with the needs of under-resourced players, which found other investors through local and international collaborations, and compete in the international stem cell therapy and banking market. Small LMICs entering the stem cell science scene only gradually develop their scientific and regulatory capacity, mainly by focusing on and protecting a few pioneering institutions, while opening up the country to foreign investors. In scientifically ambitious and advanced medium-sized countries the regulation of RM has changed radically, and no longer requires strict criteria before marketing. This change is pushed by the desire to see investment yield clinical applications rapidly, and pulled by the competition faced by countries that hitherto have traditionally defined the conditions of innovation in RM.

#### 4. International stem cell organisations and networks

Regulatory diversity regarding translational stem cell science has led to initiatives aimed to harmonise international regulation and standards. They not only facilitate exchanges in scientific knowledge, but also funnel and discipline their membership by stipulating ethical review, scientific protocols and common scientific standards. Examples of such organisations are the Alliance for Harmonisation of Cellular Therapy Accreditation (AHCTA), the International Consortium of Stem Cell Networks (ICSCN, 2004, Montreal),<sup>10</sup> the International Society for Stem Cell Research (ISSCR), the International Society for Cellular Therapy (ISCT, 1992), the International Stem Cell Forum (ISCF),<sup>11</sup> and the International Stem Cell Initiative (ISCI, affiliated to the ISCF). Regional networks, such as the Stem Cell Network (Canada), Eurostemcell and Stem cell Network Asia Pacific (SNAP, 2007) also encourage standardisation, collective policy-making and collaboration.<sup>12</sup> Initiatives focusing on biobanking, such as the International Stem Cell Registry (ISCR),<sup>13</sup> the European hESCreg,<sup>14</sup> the European bank for iPS cells (EBiSC, March 2014),<sup>15</sup> and the International Stem Cell Banking Initiative

<sup>9</sup> <http://english.vietnamnet.vn/fms/science-it/71113/growing-stem-cells-a-new-profitable-business-in-vietnam.html>; <http://www.unistemcells.com/en/patientstory/Parkinson7614015300.htm>; <http://www.asianstemcells.com/>; <http://corporate.kencare.com.sg/home/english/news/Ms-Nguyen-Thi-Ngoc-Anh.164.html>.

<sup>10</sup> [http://www.stemcellconsortium.org/uploads/documents/Montreal\\_White\\_Paper.pdf](http://www.stemcellconsortium.org/uploads/documents/Montreal_White_Paper.pdf).

<sup>11</sup> <http://www.stem-cell-forum.net/>.

<sup>12</sup> <http://www.eurostemcell.org/stem-cells>.

<sup>13</sup> <http://www.umassmed.edu/isr/stemcellethics.aspx>.

<sup>14</sup> <http://www.hescreg.eu/about>.

<sup>15</sup> <http://www.ebisc.org/>.



**Table 2**  
Factors underpinning national home-keeping policies.

Large country size and centralised accumulation of resources	Enable large-scale investment scientific fields, but facilitates regional diversity and hinders regulatory implementation
Established traditions of governing RM	Institutional stickiness can hinder radical change
High healthcare demand	High demand for treatment as push factor of scientific application
RM as economic growth tool	Encourages regulation that allows competitive applications
Position in the international science community	Scientifically advanced and independent research communities can afford to develop their own regulatory style

(ISCB)<sup>16</sup> share these ambitions. In reaction to dominant international scientific standards and restrictive national home-keeping policies, a number of initiatives aim to legitimise stem cell treatments with high patient demands that have not been recognised by international stem cell institutions. These initiatives are characterised by different degrees of size, ranging from global to local. We here discuss some initiatives from Asia, which are not necessarily representative of all those diverging from the dominant stem cell regimes described above.

The International Cellular Medicine Society (ICMS, Salem, Oregon) has 3500 physicians and patients in 35 countries with chapters in China, Peru, Mexico, Argentina and Venezuela. ICMS developed its own guidelines,<sup>17</sup> an IRB, and an international physician and patient network, and it forged collaboration with AABB (American Association of Blood Banks),<sup>18,19</sup> The ICMS announced a framework for the clinical translation of cell-based therapies, focusing on establishing standards and guidelines for studies that fall outside the jurisdiction of the FDA. However, after acrimonious debate and an FDA audit in 2012, ICMS had to close its IRB.<sup>20</sup> Nevertheless, the AABB Center for Cellular Therapies continues to be highly influential as an accreditor,<sup>21</sup> a service used by companies in Thailand, China and India to advertise their international reputation.<sup>22</sup>

The China SCI-Net, largely funded by a Hong Kong charity and linked to SCI USA, involves a transnational collaboration that aims to bridge efforts across diverging regulatory requirements, scientific practices, and interests. China SCI-Net aims to find spinal cord injury treatment using lithium and cord blood cells in a fast and safe way, involving more than 20 leading clinical centres in Mainland China, Hong Kong and Taiwan. It conducts trials through local hospitals whose staff were trained to follow the Net's own protocol.<sup>23</sup> The configuration of international skills, training, patient network, funding and local regulation has its own dynamics through which it develops standards that chime with the national situations it works in (Rosemann, 2014).

The International Association of Neurorestoratology (IANR), set up in 2004 in China, is a broad professional platform of academic exchange for scientific researchers and clinicians from over 30 countries working in the neurorestoratological field, including neurology, orthopaedics, rehabilitation, cell transplantation, Chinese traditional medicine and psychiatry. It develops its own protocols for conducting clinical trials to evaluate the safety and efficacy of its neurorestorative therapies, the establishment of validated

outcome measures, and ethical treatment of patients.<sup>24</sup> IANR uses its own form of 'self-assessment' as one of the criteria for success.<sup>25</sup>

The Guangzhou Stem Cell and Regenerative Medicine Alliance includes 18 research institutes, hospitals and companies in Guangzhou Province, and aims to further basic stem cell science, share resources and to develop translational stem cell research activities and applications.<sup>26</sup> A scientist related how the Alliance established its own rules for the clinical translation of stem cell products to respond to patient demands and local investors, but was forced to cease treatment provision.<sup>27</sup>

The Cellular Biomedicine Group Inc. (CBMG) of Shanghai, which has recently reported on the completion of a phase II stem cell trial for knee osteoarthritis (KOA), claimed to follow 'international' standards.<sup>28</sup> Since the government has prohibited treatments using unauthorised stem cell products, 'regulatory uncertainty' led CBMG to apply for marketing permission of the autologous stem cells under medical device regulation. Although this is a quick method of acquiring permission, it is limited to the hospital in which it is obtained. For this reason, a company will typically conduct multi-centre trials for a disease in a group of hospitals, and if it proves safe and efficacious, receive permission to sell in these hospitals.

The exemplified organisations illustrate the existence of international organisations with contrasting aims. They look to international and local allies for support of their research methods and standards and seek shelter under the protective umbrellas of international professional communities and local business communities. But the roots and targets of these movements lie mainly in the national home-keeping policies that articulate international regulatory trends with workable rules for regulation, funding, infrastructures, and treatment on a national level.

## 5. Conclusion

As we have demonstrated, national home-keeping policies use regulation to enable translational stem cell applications despite the existence of international authorities such as the ISSCR. As a heuristic tool, the concept calls for attention to how countries formulate stem cell policies through locally available political and regulatory mechanisms to articulate circumstances at home with global regulatory trends: governments can alter the status of national and local regulation; use various kinds of permissions for stem cell studies, trials, and provision; create regulatory clauses to make spaces for experimentation; allow hidden deployment of unauthorised therapies, and accelerate pathways to the marketing of stem cell products. The implementation, understanding and use of regulation are modulated by variable infrastructures and institutional cultures conditioning science production and the provision of therapies. Our research categorises countries' regulatory dynamics from 2008 until 2014 as adjusting, radical, beginning and

<sup>16</sup> <http://www.stem-cell-forum.net/initiatives/international-stem-cell-banking-initiative/>.

<sup>17</sup> <http://www.cellmedicinesociety.org/icms-guidelines>.

<sup>18</sup> <http://www.aabb.org/pressroom/pressreleases/Pages/pr111021.aspx>.

<sup>19</sup> <http://www.aabb.org/pressroom/pressreleases/Pages/pr120530.aspx>.

<sup>20</sup> Knoepfler Lab Stem Cell Blog, posted on 10 May 2014: <http://www.ipscell.com/tag/international-cellular-medicine-society/>.

<sup>21</sup> <http://www.aabb.org/aabbcc/Pages/default.aspx>.

<sup>22</sup> For instance, Jiangsu Beike Bio-Technology Co., Ltd; Lifecell International Pvt. Ltd., Chennai prominently advertise their AABB accreditation for somatic cell facilities.

<sup>23</sup> [http://www.chinascinet.org/index.php?option=com\\_content&task=view&id=23&Itemid=53](http://www.chinascinet.org/index.php?option=com_content&task=view&id=23&Itemid=53).

<sup>24</sup> <http://www.ianr.org.cn/English/index.asp>.

<sup>25</sup> <http://advancedneuroscience.wordpress.com/stem-cell-treatment-in-malaysia/>.

<sup>26</sup> [www1.gzbio.org/exf/GSRC/union1.htm](http://www1.gzbio.org/exf/GSRC/union1.htm).

<sup>27</sup> <http://www.gzbio.org/>.

<sup>28</sup> <http://www.bioworld.com/content/cbmg-taking-chinas-stem-cell-industry-international-stage-0>.

impasse (Table 1) and correlates these different modes of regulatory home-keeping with a country's ability to accumulate resources, country size, healthcare demands, established traditions of scientific governance, and economic and scientific ambitions. This categorisation, in turn, embodies the differences between what are regarded as large LMICs (China and India), small LMICs (Malaysia, Vietnam), traditionally dominant confederates (EU and USA) and advanced Asian countries (Japan and South Korea).

Regulatory diversity, we argued, has led to the emergence of international organisations that promote dominant forms of ethical review, scientific protocols and common scientific standards on regional and international levels. This and dissatisfaction with national home-keeping policies has also led to the formation of transnational scientific collaborations and networks that champion and practise 'alternative' therapeutic practices and evaluation methods. We argued that it is misleading to represent this friction as a binary between bona fide scientists and rogue scientists. In general, the globalisation of stem cell science has created a greater overall need to confirm compliance with globally dominant standards and regulation. It is the diversity of ways in which countries formulate and enforce these standards through their own regulatory boundary work, which is at stake.

In contrast with studies that frame translational stem cell science in terms of bona fide and rogue practices and Western (or international) versus local, this study on national home-keeping shows that 'international regulation' can be a flag proudly carried by privileged bearers, while masking extreme regulatory variation. Although notions of hegemony are relevant here, they cannot explain the difference between and within countries. Discourses on the effects of neoliberalism turn LMICs into followers of 'capital', rather than count them as important international actors, and tend to discuss regulatory friction in terms of ethics and values. By contrast, the notion of national home-keeping sheds light on regulatory agency, explaining the enabling and debilitating effects of regulatory stalemates experienced in China and India; the gradual regulatory reforms in the USA and the EU; the radical regulatory changes in South Korea and Japan; and the 'international' regulation adopted and violated by relative newcomers in the field, such as Malaysia, Thailand and Vietnam. In brief, the notion can help us understand how some countries concurrently follow and resist international regulation in the context of transnational collaborations as well as why national governments deploy strategies that appear to follow 'international regulation' to some extent, and at the same time violate and infringe it.

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## Appendix. Interviews (2012–2015)

**Table 3**

Number of interviews per country and per category.

	China	India	Japan	Malaysia	South Korea	Taiwan	Thailand	Vietnam	UK	Totals
Company Managers	2	6	4	2	8	8		12	4	46
Medical Professionals	11	12	5		9	5		12	6	60
Patients	14	15	30		25	4	1		5	94
Regulators	1	6	3	2	5	2	2		8	29
Scientists	20	19	31	3	9	4	15	11	3	115
Totals	48	58	73	7	56	23	18	35	26	345

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